An Analysis of the Effects of Acetylcholine on Conduction and Refractoriness in the Rabbit Sinus Node

ERIC N. PRYSTOWSKY, AUGUSTUS O. GRANT, ANDREW G. WALLACE, AND HAROLD C. STRAUSS

SUMMARY The effects of acetylcholine (ACh) on sinus node automaticity, atrio-sinus conduction, and refractoriness were studied in 41 isolated rabbit right atrial preparations. Average control rate was 126 beats/min, and ACh $5 \times 10^{-8}$ M, $5 \times 10^{-7}$ M, and $5 \times 10^{-6}$ M significantly decreased heart rate by 7, 15, and 43%, respectively ($P < 0.01, 0.001$, and $0.001$). Atrio-sinus conduction time at a pacing cycle length of 400 msec did not significantly change during exposure to ACh $5 \times 10^{-8}$ and $5 \times 10^{-7}$ M. However, the mean effective refractory period (ERP) of the sinus node, at a pacing cycle length of 400 msec, increased from $183 \pm 16$ msec to $210 \pm 24$ msec during exposure to ACh $5 \times 10^{-6}$ M ($P < 0.025$). The change in ERP followed the change in action potential duration. In contrast to the lack of effect of ACh $5 \times 10^{-7}$ M on atrio-sinus conduction time, ACh $5 \times 10^{-6}$ M caused 2:1 atrio-sinus block in 8 of 10 experiments. The site of block was identified using multiple microelectrode impalements, and occurred between the perinodal fibers bordering on the edge of the sinus node and the pacemaker area in the sinus node proper. When the pacing cycle length was increased and 1:1 atrio-sinus conduction was present, conduction time did not significantly differ from control. At this longer pacing cycle length the mean ERP of the sinus node was $380 \text{msec}$ greater than control and lasted well after repolarization was completed. Thus, atrio-sinus block during exposure to ACh $5 \times 10^{-6}$ M resulted from a marked prolongation of refractoriness. 

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RECENT interest in sinus node function in man has led to an increasing awareness of the importance of vagal tone as a factor that modulates the degree of disturbance of nodal function (Dighton, 1974, 1975; Strauss et al., 1977; Jordan et al., 1978). The arrhythmias resulting from such a disturbance of nodal function include sinus bradycardia, sinus pause or arrest, and sinoatrial exit block. These arrhythmias could result from a disturbance of sinus node automaticity and/or sinoatrial conduction.

Prior in vitro studies have demonstrated that acetylcholine (ACh) can depress sinus node conduction as well as sinus node automaticity (Hoffman and Cranefield, 1960; West et al., 1954, 1956; Trautwein, 1963), but neither the underlying mechanism(s) nor the site(s) of the conduction disturbance were identified. The time taken for an impulse to conduct between two points in cardiac tissue is determined by the degree of recovery from refractoriness as well as the basal or minimum conduction time (Ferrier and Dresel, 1974). Therefore, either prolongation of refractoriness or lengthening of the basal conduction time could result in a slowing of conduction. Since ACh has been shown to lengthen refractoriness in the atrioventricular node (Hoffman and Cranefield, 1960; Trautwein, 1963; Cranefield et al., 1959; Paes de Carvalho, 1966), similar changes in refractoriness could account for the conduction disturbances in the sinus node.

The effects of vagal stimulation on heart rate have been determined in man and dog (Levy et al., 1969; Eckberg, 1976). When studying the effects of ACh on the sinus node by correlating changes in electrophysiological properties with changes in spontaneous cycle length, one can determine whether the changes are occurring at concentrations of ACh that are comparable to those concentrations which are likely to be reached during vagal stimulation. Therefore, the purpose of this study was to determine the effect of graded concentrations of acetylcholine on sinus node automaticity as well as on conduction and refractoriness. In addition, when conduction failed, the site of block was identified by performing multiple microelectrode impalements in the sinus node and perinodal fiber zone.

Methods

Forty-one rabbits (1.5-2.0 kg) were anesthetized with sodium pentobarbital (35-50 mg/kg, iv), and their hearts were rapidly removed and dissected in cool, modified Tyrode's solution. The right atrium, including the sinus node but excluding the atrioventricular node, was dissected free and pinned with...
EFFECTS OF ACh ON CONDUCTION AND REFRACTORINESS/Prystowsky et al. 113

the endocardial surface uppermost to the wax bottom of a Lucite chamber.

The modified Tyrode's solution had the following composition (in mM): NaCl, 130.0; KCl, 4.0; NaH₂PO₄, 1.8; CaCl₂, 2.7; MgCl₂, 0.5; dextrose, 5.5; and NaHCO₃, 18.0; in deionized, distilled water. The solution was gassed with a 95% O₂-5% CO₂ gas mixture in the reservoir bottles, and the tissue preparation was superfused at approximately 10 ml/min. The bath fluid was maintained at a temperature of 36.0 ± 0.5°C. (35.5-36.5°C).

A stock solution of ACh was prepared by dissolving powdered acetylcholine chloride (Sigma Chemical Co.) in deionized, distilled water. ACh from the stock solution was added directly to the Tyrode's reservoir bottles to provide concentrations ranging from 5 × 10⁻⁶ to 5 × 10⁻⁸ M.

Transmembrane potentials were recorded through glass microelectrodes, and bipolar surface electrograms were recorded from the right atrial appendage and upper end of the crista terminalis as previously described (Miller and Strauss, 1974). A stimulating bipolar silver electrode was placed on the crista terminalis; stimuli were rectangular, constant-voltage 2-msec pulses, which were 1.5 times diastolic threshold.

After dissection, each preparation was allowed to stabilize until the spontaneous cycle length reached a steady state value; for most preparations an interval of approximately 30 minutes was required for stabilization. Microelectrode recordings then were obtained from cells of the sinus node, perinodal fibers, crista terminalis, or atrium (Strauss and Bigger, 1972). To identify the pacemaker site, the endocardial surface of the isolated rabbit right atrium was paced at a constant cycle length, and the tissue preparation was searched systematically to find cells demonstrating true pacemaker activity (Miller and Strauss, 1974), and in any given preparation this area was quite small. The cell giving rise to the longest antegrade conduction time (to the crista terminalis) was selected as being representative of the crista terminalis; stimuli were rectangular, constant-voltage 2-msec pulses, which were 1.5 times diastolic threshold.

After dissection, each preparation was allowed to stabilize until the spontaneous cycle length reached a steady state value; for most preparations an interval of approximately 30 minutes was required for stabilization. Microelectrode recordings then were obtained from cells of the sinus node, perinodal fibers, crista terminalis, or atrium (Strauss and Bigger, 1972). To identify the pacemaker site, the endocardial surface of the isolated rabbit right atrial preparation was searched systematically to find cells demonstrating true pacemaker activity (Miller and Strauss, 1974), and in any given preparation this area was quite small. The cell giving rise to the longest antegrade conduction time (to the crista terminalis) was selected as being representative of the electrocardial activation wavefront and activated last (Sano and Yamagishi, 1965). The nonlinear nature of nodal activation precluded use of the standard definition of effective refractory period, and the definition was therefore modified. Atrial premature depolarizations either gain access to the sinus node and reset it, or are blocked, and interpolation occurs. The effective refractory period of the pacemaker unit in the sinus node may be defined as the longest interpolated atrial response (Childers et al., 1973; Strauss and Geer, 1977). In five experiments, the crista terminalis was paced at a constant cycle length, and premature stimuli were introduced after every 12th paced beat. The crista terminalis electrogram and sinus node action potential recordings then were analyzed, and we determined that interpolated sinus node responses, occurring at the longest atrial coupling interval, were associated with sinus node action potentials whose amplitude approximated one-third of control amplitude. Therefore, the effective refractory period of the sinus node and perinodal fibers was defined as the shortest coupling interval of a crista terminalis premature depolar-
zation that resulted in a premature action potential (sinus node or perinodal fiber) whose amplitude exceeded one-third of control amplitude.

Results

Spontaneous Cycle Length

The mean spontaneous cycle length (SCL) for all preparations (n = 37) was 475 msec (range, 397–609 msec). During exposure to ACh $5 \times 10^{-8}$ to $5 \times 10^{-6}$ M, there was a significant increase in SCL at each concentration studied (Fig. 1); the increase in SCL was 35, 72, and 203 msec ($P < 0.01$, $0.001$, $0.001$) for $5 \times 10^{-8}$, $5 \times 10^{-7}$, and $5 \times 10^{-6}$ M, respectively.

Atrio-Sinus Conduction Time

Retrograde sinus node (atrio-sinus) conduction time during pacing at a cycle length of 400 msec was studied in 26 experiments. During exposure to ACh $5 \times 10^{-8}$ (n = 5) and $5 \times 10^{-7}$ M (n = 11), there was no significant change in mean atrio-sinus conduction time from control values (39 ± 6 msec, n = 16) (mean ± SE). In contrast, ACh $5 \times 10^{-6}$ M caused 2:1 atrio-sinus block in eight of 10 experiments. In the two experiments in which 1:1 atrio-sinus conduction persisted at a pacing cycle length of 400 msec (ACh $5 \times 10^{-6}$ M), the atrio-sinus conduction time increased by 19 and 36 msec.

Refractory Period

Sinus Node

The effects of ACh on the effective refractory period of the sinus node were evaluated in 31 experiments. In the presence of ACh $5 \times 10^{-8}$ M (n = 5), there was no significant change in the effective refractory period ($160 \pm 15$ msec control vs. $163 \pm 13$ msec with ACh). In contrast to the effects on the crista terminalis and atrial fibers, in which the effective refractory period decreased (vide infra), ACh $5 \times 10^{-7}$ M caused a significant increase in the effective refractory period of the sinus node, from $183 \pm 16$ msec to $210 \pm 24$ msec ($P < 0.025$) (Fig. 2; Table 1). As can be seen in Table 1 and Figure 3, a uniform increase in effective refractory period did not occur. To determine whether the effect of ACh on the refractory period was dependent on the pacemaker site within the sinus node, as determined by microelectrode recording, the change in effective refractory period from control values during exposure to ACh $5 \times 10^{-6}$ M was plotted as a function of the distance from the crista terminalis to the pacemaker site. During exposure to ACh $5 \times 10^{-6}$ M, 2:1 atrio-sinus block occurred in eight of 10 experiments. In these eight experiments, the pacing cycle length of

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** A dose-response curve for acetylcholine (ACh) on sinus node cycle length. The increase in mean value of spontaneous cycle length (SCL) over control values (ordinate) is plotted as a function of the different molar concentrations of ACh. Statistical analyses were performed by using the paired t-test to compare values of spontaneous cycle length recorded under control conditions and during exposure to acetylcholine. Separate control values were used for statistical analyses at each concentration of acetylcholine. Data are represented as mean ± SE.

![Figure 2](http://circres.ahajournals.org/)

**Figure 2.** Effects of ACh $5 \times 10^{-7}$ M on the sinus node effective refractory period in a typical experiment. The sinus node transmembrane potentials and crista terminalis electrogram recordings were retraced and are shown in the top and bottom traces of both panels. During control conditions, the effective refractory period is 215 msec. In the presence of ACh $5 \times 10^{-7}$ M, the effective refractory period is 240 msec.
Effects of ACh on Conduction and Refractoriness/Prystowsky et al.

400 msec then was increased, and 1:1 conduction returned at a pacing cycle length of 625–780 msec. When the atrio-sinus conduction time then was compared to control values, no significant difference was observed. At the longer pacing cycle length, the mean effective refractory period was 380 msec greater than control values. In the two experiments in which 1:1 atrio-sinus conduction persisted at a pacing cycle length of 400 msec, the sinus node recording site was very close to the perinodal fiber zone.

To determine whether ACh also affected the relative refractory period of the sinus node, the atrio-sinus conduction time was plotted as a function of the premature beat coupling interval. The data from a typical experiment are illustrated in Figure 5. For premature beats with coupling intervals greater than 340 msec, there was no difference in atrio-sinus conduction time between control values and those values obtained during exposure to ACh $5 \times 10^{-7}$ M. However, as the premature beat coupling interval decreased to values less than 340 msec, there was a progressive increase in the atrio-sinus conduction time over control values. This change in atrio-sinus conduction time for premature beats elicited during the relative refractory period in the presence of ACh was seen only in those experiments in which the pacemaker cell was more than 2.0 mm from the crista terminalis and in which this concentration of ACh caused a substantial increase in effective refractory period.

The mechanisms for the effect of ACh on the effective refractory period of the sinus node were
investigated by examining the relationships between the change in effective refractory period and the change in action potential duration (Fig. 6), and the amplitude of phase O of the premature response and the coupling interval (Fig. 7). During exposure to ACh, the changes in effective refractory period tended to follow changes in action potential duration (Fig. 6). In contrast to the findings for the atrial, crista terminalis, and perinodal fibers, action potential duration in pacemaker cells actually increased in most experiments (Fig. 6). For ACh, 5 x 10^{-7} M did not substantially change from control values. Thus, in contrast to the sinus node, ACh 5 x 10^{-7} M did not substantially alter the recovery of phase O amplitude until the premature beat coupling interval exceeded 550 msec. At premature beat coupling intervals exceeding 590 msec, the premature action potential amplitudes equaled control values. Since action potential duration was 164 msec during exposure to ACh, the recovery of phase O amplitude for premature responses occurred well after repolarization was completed. Hence, the disparity between action potential duration and time to full recovery was markedly increased by ACh.

**Perinodal Fibers**

The effect of ACh on the effective refractory period of the perinodal fiber zone was studied in nine experiments. The mean control effective refractory period for all experiments was 115 ± 5 msec. In the presence of ACh 5 x 10^{-7} M (n = 4), and 5 x 10^{-8} M (n = 3), there was a decrease in mean effective refractory period of 7, 7, and 10 msec, respectively.

To study the effects of ACh on the relative refractory period, the conduction time from the crista terminalis to the perinodal fiber recording site was plotted as a function of the premature beat coupling interval. The results from a typical experiment are shown in Figure 5. In contrast to the experiments on the sinus node, under control conditions there was minimal change in the conduction time as the premature beat coupling interval decreased, and a small increase in conduction time was seen only at very short premature beat coupling intervals. During exposure to ACh, there was only minimal change from control values. Thus, in contrast to the sinus node, ACh 5 x 10^{-7} M did not substantially alter the recovery of phase O amplitude.

**Figure 5** Plot of retrograde conduction time as a function of the premature beat coupling interval under control conditions and during exposure to ACh 5 x 10^{-7} M. The ordinate represents the conduction time from the crista terminalis to the sinus node or perinodal fiber recording site, and the abscissa represents the crista terminalis premature beat coupling interval (CT_{1}-CT_{2}). In the sinus node (San) study, under control conditions (□) there is an increase in retrograde conduction time from baseline values for premature beat coupling intervals less than 340 msec. During exposure to ACh (○), there is a progressive increase in conduction time for premature beats, and the effective refractory period increases by 51 msec. In the perinodal fiber (PNF) study, under control conditions (▲) there is an increase in retrograde conduction time from baseline values for premature beat coupling intervals less than 165 msec. During exposure to ACh (△), there is minimal change in retrograde conduction time and effective refractory period from control values.

**Figure 6** Change in effective refractory period as a function of change in action potential duration during exposure to ACh 5 x 10^{-7} M. Each point on the graph represents a separate experiment. The ordinate represents the change from control values in effective refractory period (Δ ERP). The abscissa represents the change from control values in action potential duration (Δ APD). The change in ERP tended to follow the change in APD.
Figure 7  Amplitude of the premature sinus node action potential as a function of the crista terminalis premature beat coupling interval. The ordinate represents the amplitude of the premature sinus node action potential, and the abscissa represents the premature beat coupling interval (CT/CTi). Broken lines represent the effective refractory period. A: The relationship between phase 0 amplitude and CT/CTi during ACh 5 × 10⁻⁷ M is only affected for early premature beats, and the effective refractory period increases from 215 msec to 240 msec. B: The relationship between phase 0 amplitude and CT/CTi during ACh 5 × 10⁻⁷ M is markedly affected, so that the return of phase 0 amplitude to control values is markedly delayed. At this concentration of acetylcholine and at a pacing cycle length of 400 msec, 2:1 atrio-sinus block occurred. At a pacing cycle length of 630 msec, 1:1 conduction was present, and at this pacing cycle length the effective refractory period was 550 msec.

Localization of Site of Conduction Disturbance

To localize the site of the conduction disturbance, we recorded transmembrane action potentials in four different experiments at multiple sites along a line perpendicular to the crista terminalis that extended through the perinodal fiber zone and sinus node (Fig. 8A). To establish the position of the different cell types relative to the crista terminalis, multiple impalements were made under control conditions during spontaneous rhythm, and the position of the microelectrode that recorded action potentials that recorded action potentials typical of the pacemaker unit (site I), the edge of the node (site II), and the perinodal fiber zone (site III) are shown in Figure 8A. The pacemaker cell (site I) was impaled again, and the preparations were exposed to ACh 5 × 10⁻⁶ M; at a pacing cycle length of 400 msec, 2:1 atrio-sinus block occurred. The microelectrode was then moved in 0.10- to 0.15-mm increments toward the crista terminalis. Phase 0 amplitude of the transmembrane action potential of the conducted and blocked impulses recorded at a pacing cycle length of 400 msec at each of the impalement sites was measured. When phase 0 amplitude of the blocked impulse relative to that of the conducted impulse was plotted as a function of the recording site, the relationship shown in Figure 8B was obtained. In the pacemaker cell, phase 0 amplitude of the blocked impulse was 20% of the conducted impulse, and near the edge of the node, phase 0 amplitude was 75% of the conducted impulse. In the perinodal fiber zone nearby, all of the impulses were conducted. Our data indicate that block occurred somewhere between sites I and III, because progressively smaller amplitude potentials were recorded as the microelectrode was moved toward the pacemaker area. The mechanism underlying the conduction block is illustrated in Figure 8C. Here the pacing cycle length was increased until 1:1 conduction resumed, in this experiment to 780 msec. The amplitude of phase O of the premature response relative to the basic response at a pacing cycle length of 780 msec is illustrated for different premature responses at sites I, II, and III (Fig. 8C). As can be seen, for coupling intervals less than 780 msec, phase O of premature responses was smaller in amplitude in the pacemaker cell than in cells nearer the edge of the node and much smaller than in the perinodal fibers. These data indicate that, during exposure to ACh, refractoriness in the sinus node was markedly prolonged relative to that in the perinodal fibers, and within the node, refractoriness was prolonged to a greater extent in the pacemaker area than at the edge of the sinus node.

Crista Terminalis and Atrium

The effects of ACh on the effective refractory period of the crista terminalis were studied in 17 experiments (Table 2; Fig. 3). The control effective refractory period was 85 ± 3 msec for the different studies (n = 17). During exposure to ACh 5 × 10⁻⁸, 5 × 10⁻⁷, and 5 × 10⁻⁶ M, the mean effective refractory period decreased from 87 to 85 msec (P < 0.05),

affect retrograde conduction time during the relative refractory period of the perinodal fiber zone.
from 86 to 72 msec ($P < 0.001$), and from 82 to 58 msec ($P < 0.001$), respectively. The changes in effective refractory period closely followed the changes in action potential duration, as the mean action potential duration decreased by 7, 10, and 24 msec during exposure to ACh $5 \times 10^{-8}$, $5 \times 10^{-7}$, and $5 \times 10^{-6}$ M, respectively.

The effects of ACh on the atrium were examined in 16 experiments (Table 2; Fig. 3). The control effective refractory period for the different experiments was $91 \pm 4$ msec ($n = 16$). The effective refractory period did not change in the presence of ACh $5 \times 10^{-6}$ M; however, during exposure to $5 \times 10^{-7}$ and $5 \times 10^{-6}$ M, the mean effective refractory period decreased from 89 to 75 msec ($P < 0.05$) and from 88 to 63 msec ($P < 0.01$), respectively. The changes in effective refractory period closely followed the changes in action potential duration, as the mean action potential duration decreased by 4, 14, and 50 msec during exposure to ACh $5 \times 10^{-8}$, $5 \times 10^{-7}$ and $5 \times 10^{-6}$ M, respectively. Between the different experiments there was a much smaller variation in change in the effective refractory period of the crista terminalis and atrium than of the sinus node during exposure to ACh $5 \times 10^{-7}$ M (Table 2; Fig. 3).

**Discussion**

The most important finding of this study is the demonstration that the marked depression of conduction caused by ACh was due to an increase in refractoriness in the sinus node. When atrio-sinus conduction was examined under conditions that approximated steady state values, i.e., when the conduction time was at a minimum, ACh $5 \times 10^{-6}$ M had no significant effect on the conduction time. At shorter pacing cycle lengths, atrio-sinus block occurred, because the effective refractory period was so prolonged. The prolongation of the effective refractory period of the sinus node resulted from a delay in recovery of phase 0 amplitude of premature responses until well after repolarization was completed. Our data from the experiments in which multiple impalements of the sinus node and perinodal fibers were performed demonstrate that refractoriness in the sinus node was prolonged to a greater extent in the pacemaker area than at the edge of the node.

The spatial distribution in refractoriness as illustrated in Figure 8C explains why atrio-sinus block occurred at the edge of or in the sinus node, and not in the perinodal fiber zone, when a pacing cycle length of 400 msec was employed. The progressively smaller amplitude potentials that were recorded as the microelectrode was moved from the edge of the node to the pacemaker area into increasingly refractory tissue is typical of block with decremental conduction. By decremental conduction we mean that “the properties of the fiber change along its length in such a manner that the action potential becomes progressively less effective as a stimulus to the unexcited portion of the fiber ahead of it” (Hoffman and Cranefield, 1960). That the effects at this concentration of ACh may be of physiological significance is supported by studies on man and dogs that demonstrate a change in heart rate during vagal stimulation that is comparable to the change in spontaneous cycle length seen in our experiments (Eckberg, 1976; Levy et al., 1969).
Table 2 Effects of Acetylcholine on Crista Terminalis and Atrium

<table>
<thead>
<tr>
<th></th>
<th>APD Control</th>
<th>ACh 5x10^-7</th>
<th>ERP Control</th>
<th>ACh 5x10^-7</th>
</tr>
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<tbody>
<tr>
<td>Crista terminalis</td>
<td>87 ±19</td>
<td>80 ±16</td>
<td>87 ±16</td>
<td>85* ±19</td>
</tr>
<tr>
<td>Atrium</td>
<td>77 ±14</td>
<td>73 ±11</td>
<td>97 ±13</td>
<td>95 ±13</td>
</tr>
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On the other hand, the lowest concentration of ACh that demonstrated a significant increase in the effective refractory period of the sinus node was 5 x 10^-7 M. At this concentration there was a mean decrease in heart rate from 126 to 110 beats/min. In contrast to the higher concentration of ACh, the change in effective refractory period closely followed the change in action potential duration and was directly a function of the distance of the pacemaker cell from the cristal terminalis. In experiments in which the pacemaker was farther than 2.0 mm from the cristal terminalis, a notable increase in effective refractory period occurred, whereas, at less than 2.0 mm, a minimal decrease or no change in effective refractory period was observed. Thus, in the latter experiments the effect of ACh on the effective refractory period of the sinus node and perinodal fibers was similar. In contrast to the effects in the sinus node, this concentration of ACh caused a uniform decrease in effective refractory period of the cristal terminalis and atrium.

The increase in effective refractory period was a direct function of distance of the pacemaker cell from the cristal terminalis during exposure to ACh 5 x 10^-7 M, and paralleled the change in action potential duration. It is of extreme interest that ACh 5 x 10^-7 M caused an increase of the sinus node action potential duration, whereas it caused the anticipated decrease in action potential duration in crista terminalis and atrial fibers (Table 2). Since changes in the activation sequence of the sinus node have been demonstrated to cause a change in action potential duration (Miller and Strauss, 1974), such a change in the activation sequence during exposure to ACh could also explain the change in action potential duration. We attempted to minimize this variable by pacing the preparation at a constant cycle length from the cristal terminalis for determination of the effects of ACh on action potential duration. The ionic mechanisms underlying the increase in action potential duration are unknown, but the increase is surprising in that an agent that has been shown to increase K uptake in sinus node (Lipsius and Vassalle, 1977) also should have shortened the sinus node action potential. In addition, ACh 5 x 10^-6 M might decrease g_Na as well as increase g_K, as occurs in the atrium (Ikmoto and Goto, 1975; Giles and Noble, 1976; Ten Eick et al., 1976; Vassalle, 1977), and the effect on either or both of these conductances could explain the marked prolongation of the effective refractory period that occurred during exposure to this concentration of ACh.

The extrapolation of our in vitro findings to the findings of in vivo experiments may explain why vagal stimulation has been reported to shift the echo zone for beats initiating sinus node reentry to longer premature beat coupling intervals (Childers et al., 1973; Paulay et al., 1973). Here, the increase in the effective refractory period should result in a shift of the earliest premature response that reenters the sinus node to a longer coupling interval. Moreover, the marked prolongation of refractoriness in the sinus node at the higher concentration of ACh could explain why strong vagal stimulation abolished sinus node reentry in the experiments reported by Paulay et al. (1973).

In summary, atrio-sinus block induced by ACh 5 x 10^-6 M occurred because refractoriness in the sinus node was markedly prolonged. When atrio-sinus conduction was evaluated under basal conditions, 1:1 conduction resumed. Refractoriness was prolonged to a greater extent in the pacemaker area than at the edge of the node, and in these experiments block occurred between the edge of the node and the pacemaker area, and not in the perinodal fiber zone. A lower concentration of ACh (5 x 10^-7 M) also prolonged the effective refractory period, and this closely followed an increase in sinus node action potential duration. The increase in sinus node action potential duration was unexpected and occurred at a concentration of ACh that decreased action potential duration in crista terminalis and atrial fibers.
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